COMPARISON OF MRI CRITERIA FOR THE DIAGNOSIS OF MULTIPLE SCLEROSIS: ROLE OF CORTICAL LESIONS

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INTRODUCTION and PURPOSE

Due to its high sensitivity in revealing white matter (WM) lesions, MRI has been formally included in the diagnostic work-up of patients with clinically isolated syndromes (CIS) suggestive of multiple sclerosis (MS) to demonstrate disease dissemination in space (DIS) and time (DIT) and to exclude alternative diagnoses [1]. The use of MRI permits an early diagnosis of MS in CIS patients before a second clinical relapse occurs. Pathologic and MRI studies have shown that intracortical lesions (ICLs) are a prominent feature of MS [2-7], are already present in CIS patients [5], are correlated with clinical disability and cognitive impairment in patients with definite MS [8, 9]. A recent monocentric study showed that the accuracy of MRI diagnostic criteria for MS is increased when considering the presence of ICLs on baseline scans from patients at presentation with CIS suggestive of MS, with a significant improvement in specificity [10].

Aim of this study was to test the performance of different sets of imaging criteria [1,10,11], including the assessment of ICLs, for the development of MS in a multicentric cohort of CIS patients.

METHODS

Patients: Patients with CIS suggestive of MS were prospectively recruited from March 2008 to July 2015 from 5 European centers: a) the Neuroimaging Research Unit, San Raffaele Scientific Institute, Milan (Italy) (19 patients); b) the CEM-Cat, Hospital Vall d'Hebron, Barcelona (Spain) (35 patients); c) the Department of Neurology, University Medical Center, Johannes Gutenberg University, Mainz (Germany) (18 patients); d) the Clinics of Neurology and Radiology, Faculty of Medicine, University of Belgrade, Belgrade (Serbia) (81 patients); and (e) the Neurology Section, Department of Neurological and Movement Sciences, Verona, (Italy) (18 patients).

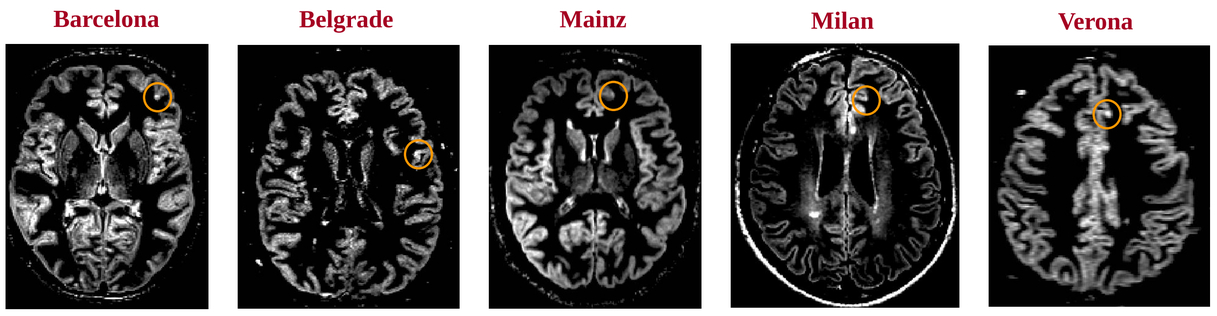
Inclusion criteria:

- A first episode suggestive of demyelination, with a careful interview to rule out possible previous events.
- A complete neurological examination with rating of the Expanded Disability Status Scale (EDSS) within 1 month from the clinical onset.
- A baseline brain (including double inversion recovery [DIR]) and spinal cord MRI scan obtained within 3 months of CIS onset.
- A follow-up (FU) brain (including DIR) scan obtained within 12 months of CIS onset.
- A clinical FU for at least 2 years or until development of clinically defined (CD) MS (defined as the occurrence during the FU of a second clinical event involving another central nervous system region after an interval of at least 1 month from the first attack) if within 2 years.
- Careful exclusion of alternative diagnoses.

MRI acquisition:

- 1.5 or 3.0 Tesla scanner (**baseline** and **within 1 year**).
- Brain MRI acquisition: (a) DIR (**Figure 1**); (b) FLAIR and/or dual-echo TSE; (c) post-contrast T1-weighted.
- Spinal cord (cervical and thoracic) acquisition: (d) STIR and/or T2-weighted; (e) post-contrast T1-weighted.

Figure 1 shows representative examples of DIR acquisitions from the different centers of the study.



MRI analysis:

- ICLs (DIR images): lesions confined to the cortical ribbon without involving the underlying subcortical WM.
- WM lesions (T2/FLAIR/STIR images): total number of lesions; number of periventricular (PV) lesions; number of juxtacortical (JC) lesions; number of posterior fossa (PF) lesions; number of spinal cord (SC) lesions.
- Count of the number of brain and SC Gd-enhancing lesions (on post-contrast T1-weighted scans).
- Count of the number of new WM lesions, new ICLs and Gd-enhancing lesions on FU MRI scans.
- Assessment of the fulfilment of the available MRI criteria for DIS (**Table 1**) from lesion classification and count.

Table 1 summarizes DIS criteria according to Revised McDonald 2005 [11], 2010 [1] and Filippi 2010 [10].

DIS Criteria		
Revised McDonald 2005	≥3 of the following:	≥ 9 T2 lesions or 1 ≥ Gd lesion
		≥3 PV lesions
		≥1 JC lesion
		≥1 PF or SC lesion
Revised McDonald 2010	≥2 of the following:	≥ 1 PV lesion
		≥ 1 JC lesion
		≥ 1 PF lesion
		≥ 1 SC lesion
Filippi 2010	≥2 of the following:	≥1 SC or ≥1 Gd lesion
		≥1 PF lesion
		≥1 ICL

Statistical analysis:

- **Evolution to MS** defined as:
  - occurrence of a second clinical event;
  - new T2/FLAIR lesions and/or new Gd-enhancing lesions.
- Identification of MRI variables independently predicting the evolution to MS using **univariate logistic regression analysis**.
- Assessment of **sensitivity**, **specificity**, **accuracy**, **positive predictive value** (**PPV**), and **negative predictive value** (**NPV**) of the different MRI criteria for DIS using the evolution to MS as outcome.

RESULTS

Figure 2 shows the flowchart of the study to reach the final cohort of CIS patients included.

	CIS patients
Barcelona	**35**
Belgrade	**81**
Mainz	**18**
Milan	**19**
Verona	**18**
	171

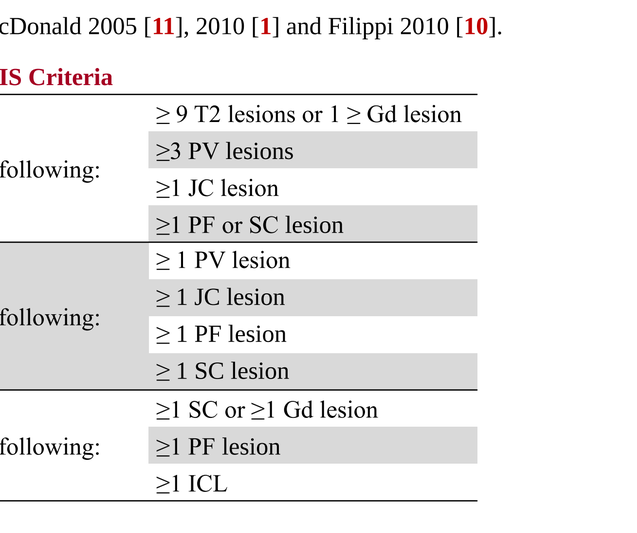
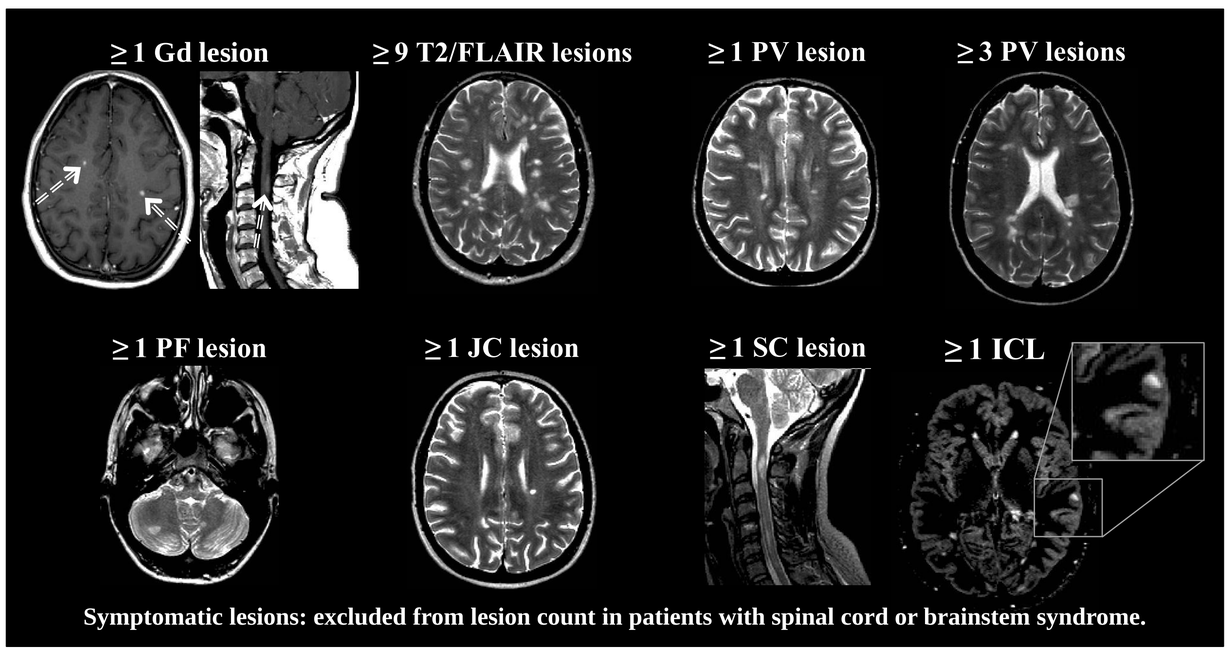


Table 2 shows the main baseline demographic, clinical, and MRI findings from the final sample of CIS patients. Eight CIS patients had normal baseline MRI scan (no lesions).

Variable	CIS Patients (n=72)
Number (%) of Men / Women	26 (36.1%) / 46 (63.9%)
Median age at onset [range] {years}	30 [20-49]
Median DD at baseline MRI [range] {months}	2.3 [0.0-3.0]
Median EDSS at baseline (SD) [range]	1.5 [0.0-3.0]
Clinical onset/ presenting symptoms (%):	
Monofocal	48 (66.7%)
• Optic neuritis	• 13 (27.1%)
• Brainstem syndrome	• 13 (27.1%)
• Spinal cord	• 10 (20.8%)
• Other	• 12 (25.0%)
Multifocal	24 (33.3%)
Median FU (SD) [range] {months}	24.2 [1.4-78.7]
CDMS at FU	48 (67.6%)
Median time to CDMS [range] {months}	14.9 [1.0-78.5]
MS at FU (CDMS and/or ≥1 new T2 lesion)	66 (91.7%)

DD=disease duration;
SD=standard deviation;
FU=follow-up.

MRI criteria: **Figure 3** shows examples of the different individual criteria assessed for the definition of DIS according to Revised McDonald 2005 [11], 2010 [1] and Filippi 2010 criteria [10].



Univariate logistic regression analysis: **Table 3** shows the results of the univariate analysis for each single DIS MRI criteria evaluated.

	Univariate analysis	
Variable	**OR (95% CI)**	**p value**
≥ 1 Gd lesion	6.4 *	0.07
≥ 9 T2/FLAIR lesions	3.7 (0.7-20.4)	0.13
≥ 1 PV lesion	15.5 (2.3-102.9)	**0.005**
≥ 3 PV lesions	12.7 (2.0-79.5)	**0.007**
≥ 1 PF lesion	14.4 (1.6-132.3)	**0.02**
≥ 1 JC lesion	2.8 (0.5-17.4)	0.26
≥ 1 SC lesion	1.7 (0.3-8.9)	0.55
≥ 1 ICL	3.3 (0.6-19.2)	0.19

OR= odds ratio

*=exact stimation

Performance of different criteria: **Table 4** shows the performance of the different MRI criteria for DIS in predicting the conversion to MS after 2 years of FU.

	# (%) of positive MRI*	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	OR for MS conversion (95% CI) [p value]
Revised McDonald 2005	58 (80.6%)	**0.81** (0.70-0.89)	**0.83** (0.72-0.91)	**0.50** (0.12-0.88)	**0.95** (0.86-0.99)	**0.21** (0.05-0.51)	**5.0** (0.9-28.1) [0.07]
Revised McDonald 2010	64 (88.9%)	**0.89** (0.79-0.95)	**0.92** (0.83-0.97)	**0.50** (0.12-0.88)	**0.95** (0.87-0.99)	**0.38** (0.09-0.76)	**12.2** (1.9-77.0) [**0.008**]
Filippi 2010	55 (76.4%)	**0.79** (0.68-0.88)	**0.80** (0.69-0.89)	**0.67** (0.22-0.96)	**0.96** (0.87-0.99)	**0.24** (0.07-0.50)	**8.2** (1.3-49.5) [**0.02**]

*Positive MRI indicates fulfillment of MRI diagnostic criteria for DIS at baseline MRI.

CONCLUSIONS

- **An early identification of patients with CIS at risk of developing MS is critical for an early treatment, which might modify favourably the disease course.**
- **The revisions of MRI diagnostic criteria are aimed at simplifying the lesion count-model and to allow a more accurate and earlier diagnosis of MS in CIS patients.**
- **Despite the limitations of the study, we showed that the inclusion of ICLs assessment in a large multicentric cohort of CIS patients improves specificity of the diagnostic criteria preserving sensitivity and accuracy.**
- **The detection of ICLs *in vivo* using MRI should be considered in future diagnostic algorithms for MS.**

REFERENCES

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